

Message

From: Kraft, Andrew [Kraft.Andrew@epa.gov]
Sent: 11/30/2017 2:33:10 PM
To: Subramaniam, Ravi [Subramaniam.Ravi@epa.gov]; Bussard, David [Bussard.David@epa.gov]
CC: Glenn, Barbara [Glenn.Barbara@epa.gov]; Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; Vulimiri, Suryanarayana [Vulimiri.Sury@epa.gov]
Subject: RE: Hot off the press on Endogenous Formaldehyde
Attachments: formaldehyde_assessment overview_IOAAreview_102617rssvedits.docx; Formaldehyde Main Text 102417rssvEdits.docx

Hi Ravi, good question. It is just too problematic at this point for you to be working in the master versions (on Sharepoint) that Barbara and I are working on.

So, I have attached here a current copy of the main draft and overview documents. Please crosswalk any changes across both documents, and let us know if you also need to make changes to the Appendices (which you can probably work on directly in Sharepoint, as we are not yet working on them).

Since it sounds like you will be working on making changes before Sury, we would prefer if you could make your edits in track changes and then send the docs to Sury, who can then send the docs back to us (or something similar).

Thanks!

From: Subramaniam, Ravi
Sent: Thursday, November 30, 2017 9:09 AM
To: Kraft, Andrew <Kraft.Andrew@epa.gov>; Bussard, David <Bussard.David@epa.gov>
Cc: Glenn, Barbara <Glenn.Barbara@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Vulimiri, Suryanarayana <Vulimiri.Sury@epa.gov>
Subject: RE: Hot off the press on Endogenous Formaldehyde

I have set aside some time this morning for formaldehyde, and will add this to my agenda. However, I would only add a few sentences to the bottom up part. Someone else, Sury perhaps?, needs to add, if necessary, elsewhere.

Andrew, how should I do this (and the other edits I have promised)? Directly, or send you the blurb separately?

-

Ravi.

Ravi Subramaniam
RRB 51237/ (202) 564-2445 (o), (571) 571-5711 Ex. 6 Personal Privacy (PP)

From: Kraft, Andrew
Sent: Thursday, November 30, 2017 7:56 AM
To: Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>; Bussard, David <Bussard.David@epa.gov>
Cc: Glenn, Barbara <Glenn.Barbara@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Vulimiri, Suryanarayana <Vulimiri.Sury@epa.gov>
Subject: RE: Hot off the press on Endogenous Formaldehyde

So, what do we need to add to the tox review/ appendices/ overview to close the loop?

Thanks for sharing, Sury!

From: Subramaniam, Ravi

Sent: Thursday, November 30, 2017 7:26 AM

To: Bussard, David <Bussard.David@epa.gov>

Cc: Kraft, Andrew <Kraft.Andrew@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>

Subject: Re: Hot off the press on Endogenous Formaldehyde

Ex. 5 Deliberative Process (DP)

--Ravi.

Ravi Subramaniam, Ph.D.

Chief, Toxic Effects Branch, IRIS, NCEA, EPA

RRB 51237/ (202) 564-2445 (O) Ex. 6 Personal Privacy (PP)

On Nov 30, 2017, at 7:04 AM, Bussard, David <Bussard.David@epa.gov> wrote:

Ravi

Ex. 5 Deliberative Process (DP)

David Bussard

Begin forwarded message:

From: "Vulimiri, Suryanarayana" <Vulimiri.Sury@epa.gov>

Date: November 29, 2017 at 5:39:41 PM EST

To: "Bussard, David" <Bussard.David@epa.gov>

Subject: RE: Hot off the press on Endogenous Formaldehyde

David, that is the question I have. It needs some collective thinking into it. Here are some preliminary thoughts.

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Sury

Sury Vulimiri, Ph.D., DABT National Center for Environmental Assessment, Office of Research & Development, US EPA. Phone: 919-541-3558 | Fax: 919-541-0245 | vulimiri.sury@epa.gov

From: Bussard, David
Sent: Wednesday, November 29, 2017 5:06 PM
To: Vulimiri, Suryanarayana <Vulimiri.Sury@epa.gov>
Subject: RE: Hot off the press on Endogenous Formaldehyde

Thanks Sury

What do you think this means for the role of endogenous formaldehyde in assessing the risk of inhaled formaldehyde?

David

From: Vulimiri, Suryanarayana
Sent: Wednesday, November 29, 2017 4:43 PM
To: Bateson, Thomas <Bateson.Thomas@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Fritz, Jason <Fritz.Jason@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Makris, Susan <Makris.Susan@epa.gov>; Segal, Deborah <Segal.Deborah@epa.gov>; Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>; Vulimiri, Suryanarayana <Vulimiri.Sury@epa.gov>; Whalan, John <Whalan.John@epa.gov>
Cc: Bussard, David <Bussard.David@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>
Subject: Hot off the press on Endogenous Formaldehyde

Nature. 2017 Aug 31;548(7669):549-554. doi: 10.1038/nature23481. Epub 2017 Aug 16.

Mammals divert endogenous genotoxic formaldehyde into one-carbon metabolism.

Burgos-Barragan G¹, Wit N¹, Meiser J², Dingler FA¹, Pietzke M², Mulderrig L¹, Pontel LB¹, Rosado IV³, Brewer TF⁴, Cordell RL⁵, Monks PS⁶, Chang CJ¹, Vazquez A², Patel KJ^{1a}.

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Abstract

The folate-driven one-carbon (1C) cycle is a fundamental metabolic hub in cells that enables the synthesis of nucleotides and amino acids and epigenetic modifications. This cycle might also release formaldehyde, a potent protein and DNA crosslinking agent that organisms produce in substantial quantities. Here we show that supplementation with tetrahydrofolate, the essential cofactor of this cycle, and other oxidation-prone folate derivatives kills human, mouse and chicken cells that cannot detoxify formaldehyde or that lack DNA crosslink repair. Notably, formaldehyde is generated from oxidative decomposition of the folate backbone. Furthermore, we find that formaldehyde detoxification in human cells generates formate, and thereby promotes nucleotide synthesis. This supply of 1C units is sufficient to sustain the growth of cells that are unable to use serine, which is the predominant source of 1C units. These findings identify an unexpected source of formaldehyde and, more generally, indicate that the detoxification of this ubiquitous endogenous genotoxin creates a benign 1C unit that can sustain essential metabolism.

PMID:

28813411

DOI:

[10.1038/nature23481](https://doi.org/10.1038/nature23481)

<< File: Burgos-Barragan et al 2017_EndogenousFA.pdf >> << File: Pontel et al 2015_SV.pdf >>

So the bottom line is that endogenous formaldehyde is safely handled by the cells diverting it into normal cellular metabolism. This is published in Nature (PDF attached).

Does this mean there is no need to worry about endogenous formaldehyde for making any adjustments for risk assessment when dealing with exogenous formaldehyde?

One of the co-authors is Pontel, who published earlier an article titled "*Endogenous formaldehyde is a hematopoietic stem cell genotoxin and metabolic carcinogen*" in the Journal 'Molecular Cell' on which Dr. Swenberg is a co-author.

Sury

Sury Vulimiri, Ph.D., DABT National Center for Environmental Assessment, Office of Research & Development, US EPA. Phone: 919-541-3558 | Fax: 919-541-0245 | vulimiri.sury@epa.gov

